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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/211,755	12/15/98	JONES K	54002-D/JPW/

HM22/0524

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EXAMINER	
BRANNOCK,M	
ART UNIT	**PAPER NUMBER**
1646	12

DATE MAILED: 05/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/211,755	Jones, KA
Examiner	**Group Art Unit**
Michael Brannock, Ph.D.	1646

☒ Responsive to communication(s) filed on *Apr 26, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *190-249* is/are pending in the applicat

Of the above, claim(s) *190-207, 209, 211, 212, 215-220, 226, 227, 232, and 241* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *208, 210, 213, 214, 221-225, 228-231, and 233-240* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *190-249* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5-8, 11*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Status of Application Claims and Amendments

1. Claims 190-249 are pending.

2. Claims 190-207, 209, 211-212, 215-220, 226, 227, 232, and 241-249 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 11, 4/26/00. Applicant is reminded that the claims 208, 210, 213, 214, 221-225, 228-231 and 233-240 will be examined only to the extent to which they read on screening for an agonist of a $GABA_BR1/R2$ receptor, as put forth in Paper 9, 3/20/00.

3. Applicant is informed that the preliminary amendments put forth in Paper 4, 12/15/1999, and Paper 8, 2/20/00, are entered in full.

Response to Amendment

4. Applicant's election with traverse of Group II claims 208, 210, 213, 214, 221-225, 228-231 and 233-240, as the claims are directed to screening for an agonist of a $GABA_BR1/R2$ receptor in Paper No. 11, 4/26/00 is acknowledged. The traversal is on the grounds that Groups I and III-VIII are not independent and distinct from the elected Group II, and that a search of Groups I-VIII would not be a serious burden on the examiner (see Paper No. 11, 4/26/00.. This is not found persuasive for the following reasons:

Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) **or** distinct as claimed (see MPEP § 806.05- §806.05(I)): and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a)- 806.04(I), § 808.01(a), and § 808.02).

The term "distinct" means that two or more subjects as disclosed are related, for example, as combination and part (subcombination) thereof, product and process of use, process and product made, etc., but are capable of separate manufacture, use or sale as claimed, and are patentable (novel and unobvious) over each other (though they may each be unpatentable because of the prior art). It will be noted that in this definition the term related is used as an alternative for dependent in referring to subjects other than independent subjects (MPEP § 802.01). Where inventions are related as disclosed but are distinct as claimed, restriction may be proper (MPEP § 806(B)). The distinctiveness of each of Groups I-VIII, has been but forth by the examiner in Paper 9, 3/20/00.

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search. These criteria were met in the above restriction. Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. Thus, the groups require divergent searches, and to search all the inventions in a single application would be burdensome. Therefore, the restriction is maintained and made final.

Specification

5. The specification is objected to because of the following informalities:

The Brief Description of Figures 19, 20 and 21 fail to refer to the parts of the figures, e.g. Fig. 19 A-I.

Appropriate correction is required.

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons: Figure 10 makes reference to two specific sequences yet only one is accounted for in the Brief Description of the Drawings; these references must contain a sequence identifier of the form: SEQ ID NO: X. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 208, 210, 213, 214, 221-225, 228-231, 234, 236-240 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying agonists of the $GABA_BR1/R2$ receptor wherein the $GABA_BR1$ receptor is either of the splice variants disclosed by Kaupmann *et al.*, *Nature* 386(239-246)1998, referred to in the

specification on page 4, and wherein the $GABA_BR2$ receptor is either of the polypeptides disclosed in the instant application as SEQ ID NO: 2, 4, or 47, does not reasonably provide enablement for a method of identifying agonists of the $GABA_BR1/R2$ receptor wherein the receptor $GABA_BR1/R2$ comprises polypeptides other than those recited above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims encompass a $GABA_BR1/R2$ receptor composed of any polypeptides which may be deemed $GABA_BR1$ and $GABA_BR2$. Specifically, the specification contemplates splice variants of the polypeptides of the instant invention and other amino acid sequence variants (see page 29). However the specification has not put forth what the splice variants are nor what amino acid sequence substitutions, deletions, or insertions to make in the polypeptides of the instant invention.

Two splice variants of the $GABA_BR1$ receptor are known in the art as disclosed by Kaupmann *et al.*, referred to above, yet no others are known, nor are others put forth in the instant specification. Additionally, the specification does not put forth splice variants of the $GABA_BR2$ polypeptide. Applicant's disclose, and it is now well known, that the $GABA_BR1$ receptor and the $GABA_BR2$ receptor require co-expression in *in vitro* systems in order to display the properties of the native $GABA_B$ receptors (see page 5). However, it is known in that the *in vivo* distributions of $GABA_BR1$ and $GABA_BR2$ overlap but are not completely co-extensive (see Kuner *et al.* Science 283(74-77)1999, especially page 75 col 3 and page 76 cols 1 and 2; see also

Bowery *TiPS* 18(103)1997, 3rd col). These facts strongly suggest that there are other $GABA_BR$ variants, yet to be discovered, that heterodimerize with the known polypeptides, and that could also be termed $GABA_BR1$ or $GABA_BR2$. The instant claims encompass these yet to be discovered $GABA_BR$ variants, yet the specification has not taught one of skill in the art how to make them.

Additionally, the specification contemplates amino acid sequence variants of the polypeptides of the instant invention, yet the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, Applicant has not provided guidance as to what properties of the allelic variants or sequence variants of the proteins corresponding to $GABA_BR1$ or $GABA_BR2$ might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the proteins corresponding to $GABA_BR1$ or $GABA_BR$ and variants of said protein. If the variants of the proteins corresponding to $GABA_BR1$ or $GABA_BR2$ are to have a structure and function similar to the proteins corresponding to $GABA_BR1$ or $GABA_BR2$, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the proteins corresponding to $GABA_BR1$ or $GABA_BR2$.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely

complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure, pp. 14-16). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional

configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the infinite number of amino acid sequence variants encompassed by the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

9. Claims 233 and 235 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention The invention appears to employ novel nucleic acid molecules (i.e., ATCC Deposit numbers 209104 and 203515). Since the nucleic acid molecules are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the nucleic acid molecules are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the nucleic acid molecules. The specification does not disclose a repeatable process to obtain the nucleic acid

molecules and it is not apparent if the nucleic acid molecules are readily available to the public. It is noted that Applicant has deposited the nucleic acid molecules (page 33), but there is no indication in the specification as to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific nucleic acid molecules have been deposited under the Budapest Treaty and that the nucleic acid molecules will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include such, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information.

Furthermore, if the Deposit Rules requirements are to be complied with, claims 233 and 235, would be subject to the same scope of enablement rejection put forth above regarding amino acid sequence variants of a $GABA_BR1$ polypeptide.

Conclusions

10. Claims 208, 210, 213, 214, 221-225, 228-231 and 233-240 are not allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D., can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

MB

May 22, 2000